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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,897	BARKAN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8 and 28-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8, 28-35 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2-8, 28, 30-33, 37-39 have been amended. Claims 9 and 36 have been canceled. Claims 2-8, 28-35 and 36-39 are pending and under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claims 2-8, 28-35 and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 and 31 recite "stringent conditions that include washing conditions" 12-20 degrees "below the calculated Tm of the hybrid under study". The metes and bounds of said stringent conditions cannot be determined because the "hybrid under study" is itself not limited by the claim language. In order to determine what the hybrid under study consists of, it would be necessary to know the constitution of the nucleic acids which was being hybridized to the nucleic acid encoding leptin.

4. Claims 1-8, 28, 30, 31, 32, 34, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of leptin, or fragments of leptin, does not reasonably provide enablement for the administration of leptin muteins or fragments of leptin muteins or fusion proteins of leptin muteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-8, 28, 32 and 34 are method claims drawn in part to the administration of leptin muteins, or fragments of leptin muteins or fusion proteins of leptin muteins. Claims 30, 31 and 37-39 are drawn to the administration of leptin muteins. The specification is not enabling for said methods because the specification does not teach how to make said leptin muteins which would function as claimed. The specification states that preferred changes for muteins are conservative substitutions (page 9, lines 15-16). It is noted that this is a preferred embodiment and not equivalent to a claim limitation. The specification discusses general knowledge of

substitution of amino acid sequence with the goal of preserving the biological function of the molecule(page 9, lines 17-27), however, these are not specific directions for the making of leptin muteins, these teachings represent the general knowledge in the art. the specification refers to RE 33,653, US 4,959,314, US 4,588,585, US 4,737,462, US 5,116,943, US 4,965,195, US 4,879,111. After review of the aforementioned patents it is noted that none teach how to make the leptin muteins of the instant invention. Further, there are no examples presented of leptin muteins having as little as 60% , 70% or 80% identity with leptin. Without further teachings in the specification, one of skill in the art could not be assured that a leptin muteins can be made having as little as 60% , 70% or 80% sequence identity with leptin with the ability to inhibit the IGF-I induced or insulin induced proliferation of T-47D cells or MCF7 cells. Neither the definition of "mutein" nor the claim to stringent hybridization serves to define the sequence of a variant product. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al. (Journal of Cell Bio. 111:2129 2138, 1990, cited in a previous Office action), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology, 1988, Vol 8:1247 1252, cited in a previous Office action). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a variant protein that shares as little as, 60%, 70% or 80% sequence identity with leptin would even function as suggested. One of skill in the art would be subject to undue experimentation in order to find muteins and variants that function as leptin. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variants and fusion proteins thereof. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

5. Claims 2, 3, 6, 7, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (Journal of Biological Chemistry, June 14, 1996, Vol. 24, pp. 14610-14616, cited in the previous Office action) in view of Cohen et al (Science, 1996, Vol. 274, pp. 1185-1188, cited in the previous Office action)

Claim 28 is drawn in part to a method for treating or inhibiting tumors in mammals comprising administering to a mammal in need thereof an effective amount of leptin. Claim 29 embodies the method of claim 28 wherein the active agent is leptin. Claims 2 and 3 embody the method of claim 28 wherein cell proliferation is inhibited for the treatment of malignancy, and wherein growth factor-dependent tumors are inhibited, respectively. Claim 6 embodies the method of claim 28 wherein the growth stimulatory effect of insulin on tumor cells is inhibited. Claim 7 embodies the method of claim 28 wherein the mitogenic response of tumor cells to receptor kinases, growth factors and cytokines of the group consisting of IGF-1, IL-4 and Il-9 is inhibited.

Tanaka et al teach that the insulin receptor substrate is upregulated in hepatocellular tumors at both the protein and the RNA level (page 14610, second column, lines 16-29), Tanaka et al teach that hIRS-1 overexpression promotes neoplastic transformation of NIH3T3 cells and clones transfected with hIRS-1 exhibit the phenotypic properties of transformations such as foci formation, anchorage-independent cell growth in soft agar and formation of large tumors in nude mice (page 14611, first column, lines 9-15). Tanaka et al teach that hIRS-1 overexpression induces cellular transformation in an IGF-1-depdnet manner and suggest that IRS-1 signaling pathways may be involved as a general mechanism of cellular transformation in the liver (page 14614, second column, lines 12-16). Tanaka et al teach that IRS-1 is a major intracellular substrate of IGF-I and insulin receptors, and such receptors directly interact with the phosphotyrosine binding domain of IRS-1 (page 14615, first column, lines 33-36). Tanaka et al teach that IGF-1 signals have been found necessary to promote tumorgenicity in vivo and that the cellular transformation pathway may be specifically mediated through IRS-1 (page 14615, first column, lines 60-64)

Cohen et al teach that leptin downregulates the insulin-dependent tyrosine phosphorylation of IRS-1 in HepG2 cells (legend for Figure 2, lines 1-4) which is a human heptocellular carcinoma cell line. Cohen et al state that the "most profound effect of leptin was a

reduction in the amount of a tyrosine-phosphorylated 185 kD protein, identified as the insulin receptor substrate" (page 1186, second column, lines 30-33).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to administer leptin in order to reduce tyrosine phosphorylation of IRS-1 in patients having hepatocellular carcinoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Tanaka et al on the correlation between IGF-1 signaling through the phosphotyrosine binding domain of IRS-1, and the promotion of tumorigenesis in vivo mediated by hIRS-1; and the teachings of Cohen et al on the "profound" reduction in the amount of tyrosine-phosphorylated IRS-1 in hepatocellular carcinoma cell lines treated with leptin. One of skill in the art would be motivated to administer the leptin to block the tyrosine phosphorylation of IRS-1 and subsequently decrease the signaling cascade of the insulin and IGF-1 receptors.

6. Claims 2, 3, 6, 7, 28, 29, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (Journal of Biological Chemistry, June 14, 1996, Vol. 24, pp. 14610-14616) and Cohen et al (Science, 1996, Vol. 274, pp. 1185-1188) as applied to claims 2, 3, 6, 7, 28 and 29 above, and further in view of Carter et al (US 2002193571, cited in the previous Office action).

Claim 34 is drawn to the method of claim 28 in part wherein said active agent is a fusion protein comprising leptin. Claim 35 embodies the method of claim 34 wherein the active agent is a leptin fusion protein.

The combination of Tanaka et al and Cohen et al render obvious the administration of leptin for the treatment of hepatocellular cancer the reason set forth above. The combination of Tanaka et al and Cohen et al do not render obvious the administration of leptin as a fusion protein.

Carter et al teach a fusion protein, termed an immunoadhesin, comprising the OB protein and the Fc domain of an antibody [0237]. The OB protein is synonymous with leptin. Carter et al teach that the Fc regions of said immunoadhesins confer a longer half life on the OB protein [0264-0265].

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the leptin immunoadhesin for leptin in the method rendered obvious by the combination of Tanaka et al l and Cohen et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Carter et al on the increased half life conferred on leptin by fusion with the Fc domain of an antibody. One of skill in the art would be motivated to increase the in vivo half life in order to sustain the dose of leptin in vivo.

7. Applicant argues that there would be no motivation to combine the teachings in the previous references because there was no teaching in the art that breast cells contained receptors for leptin. This was considered and found persuasive. Thus, claims specifically drawn to the inhibition of breast cancer are not included in the instant art rejections. However, Cohen et al does teach that leptin is taken up by hepatocellular carcinoma cells. Thus, the above claims are rejected to the extent that they read on treating patients with hepatocellular carcinoma.

8. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/27/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER